

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-8, 35, 69-71, 73-77, and 91-113 were pending in the case at the time of the Office Action. Claims 69, 74, 91-94, 98, 103, and 109 have been amended in the Amendment set forth herein without prejudice or disclaimer. Claims 1-34, 36-68, 70-73, 78-90, and 112-113 have been canceled without prejudice or disclaimer. New claims 114-134 have been added. Thus, claims 35, 69, 74-77, 91-111, and 114-134 are currently pending.

Support for the amendments to the claims can be found generally throughout the specification, such as in the claims as originally filed. Please note that claim 69 has been amended to recite particular dyes and basic reagents, the specific surfaces set forth in claim 73, and “medical devices.” An example of support for “medical device” in claim 69 can be found on page 6, line 25 – page 7, line 8 and page 9, line 18 – page 10, line 14.

Claims 69, 74, 103, 109, 124-126, 128-129, and 134 have been amended to recite specific molar ratios of basic reagent:dye. An example of support for these limitations can be found on page 4, line 26 to page 5, line 2 of the specification and in the Examples. Claim 74 has been amended to recite specific dyes and basic reagents.

Claim 91 has been amended to recite “silk” as an alternative surface. An example of support for silk can be found on page 6, line 8, page 9, line 26, and Table 6, page 22. In claim 92, “silicone” is included as an alternative for the polymer. Support can be found on page 3, line 11, page 6, line 8, and page 9, line 25. Claim 93 has been amended to change “comprises” to “is comprised of.” Claim 94 has been amended to depend from claim 91.

Claim 98 has been amended to be in independent form.

Claim 103 has been amended to recite specific dyes and basic reagents, and specific ratio of basic reagent:dye. An example of support for the molar ratio of basic reagent:dye is as discussed above.

Regarding the medical devices set forth in claims 115-117 and 121, an example of support can be found on page 16, lines 14-20 of the specification. The remaining new claims recite specific dyes, basic reagents, and/or molar ratios, and support is as discussed above.

Applicants specifically reserve the right to prosecute any subject matter canceled from the previous set of claims in a continuation or divisional application.

B. Statement Regarding Substance of Interview

Regarding the Examiner's statement of the substance of the interview dated February 22, 2007, Applicants do not agree with the Examiner's statement that claim 98 should have been listed in the same rejection containing claim 97 over Dangman in view of Kirk-Othmer Encyclopedia because Dangman teaches the use of chlorhexidine. Applicants' response is set forth in detail below in the response to the 35 U.S.C. §103(a) rejection based on Dangman in view of Kirk-Othmer. Applicants otherwise agree with the Examiner's statement regarding the substance of the interview.

Regarding the Examiner's statement of the substance of the interview dated April 13, 2007, Applicants do not agree with the Examiner's assertion that there is functional equivalence between the proposed claimed dyes and the dyes of Dangman and Harper, and that a 103 rejection would therefore be proper. For the reasons discussed below in the response to the rejections under 35 U.S.C. §103(a), the rejections have been overcome. Applicants otherwise concur with the statement of the substance of the interview dated April 13, 2007.

C. The Claim Rejections Under 35 U.S.C. §102 Are Overcome

1. Rejections Based on Dangman *et al.*

Claims 1-2, 5-6, 35, 69-73, 91-94, 103-104, 106-107, and 112-113 are rejected under 35 U.S.C. §102(b) as being anticipated by Dangman *et al.* (U.S. Patent 5,335,373; “Dangman”). In view of the cancellation of certain claims without prejudice or disclaimer as discussed above, the only pending claims at issue in this rejection includes claims 35, 69, 91-94, 103-104, and 106-107. Applicants respectfully traverse.

In view of the Amendment set forth herein, Dangman fails to anticipate any of the claims because it does not explicitly or inherently disclose each limitation of the claimed invention. In particular, as to each of the claims at issue in this rejection, Dangman does not expressly or inherently set forth any of the combination of dyes and basic reagents set forth in the claims. As to claim 35, Applicants specifically note that Dangman fails to expressly or inherently disclose any basic reagent bound to a dye. By amending the claims in the manner set forth herein, Applicants in no way disclaim any subject matter, and reserve the right to continue to prosecute any subject matter canceled from the case in a continuation or divisional application.

Nor are any of new claims 114-134 anticipated by Dangman. Each of the new claims depends from one of independent claim 69, 74, or 103. Claims 69 and 103 are not anticipated because Dangman does not expressly or inherently set forth any of the combination of dyes and basic reagents set forth in these claims, and claim 74 was not included in this rejection.

In view of the foregoing, Dangman fails to anticipate any of claims 35, 69, 91-94, 103-104, and 106-107 or new claims 114-134. Therefore, it is respectfully requested that the rejection under 35 U.S.C. §102(b) be withdrawn.

2. Rejections Based on Harper *et al.*

Claims 1-2 and 74 are rejected under 35 U.S.C. §102(e) as being anticipated by Harper *et al.* (U.S. Patent App. Pub. No. 2005/0049306; “Harper”). In view of the cancellation of certain claims without prejudice or disclaimer as discussed above, the only pending claim at issue in this rejection is claim 74. Applicants respectfully traverse the rejection of this claim.

Harper fails to anticipate the claims as written because it does not explicitly or inherently disclose each limitation of the claimed invention. Harper does not expressly or inherently set forth any of the combination of dyes and basic reagents set forth in this claim. This claim no longer recites “indigo carmine.” By amending the claims in the manner set forth herein, Applicants in no way disclaim any subject matter, and reserve the right to continue to prosecute any subject matter canceled from the case in a continuation or divisional application.

New claims 114-134 are not anticipated by Harper because they either depend from claims 69 or 103 (which were not included in this rejection), or they depend from claim 74, which for the reasons discussed above is not anticipated by Harper.

In view of the foregoing, Harper fails to anticipate claim 74 or any of the new claims. Therefore, it is respectfully requested that this rejection be withdrawn.

D. The Rejections Under 35 U.S.C. §103(a) Are Overcome

1. Rejections Based on Dangman in View of Parikh

Claim 3 is rejected under 35 U.S.C. §103(a) as being unpatentable over Dangman as applied above and further in view of Parikh *et al.* (U.S. Patent 6,123,926; “Parikh”). Applicants respectfully traverse.

This rejection is moot because claim 3 has been canceled without prejudice or disclaimer. New claims 114-134 would not be considered as obvious over Dangman in view of Parikh because they depend from a claim that was not included in this rejection (claim 69, 74, or 103).

Therefore, this rejection is moot.

2. Rejections Based on Dangman In View of Houze

Claims 4, 95-96, 99-100, 105, and 109-111 are rejected under 35 U.S.C. §103(a) as being unpatentable over Dangman as applied above and further in view of Houze et al. (U.S. Patent App. Pub. No. 2004/0018241; “Houze”). In view of the cancellation of certain claims without prejudice or disclaimer as discussed above, the only claims at issue in this rejection include claims 95-96, 99-100, 105, and 109-111. Applicants respectfully traverse the rejection of these claims.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) the prior art references must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and (3) there must be a reasonable expectation of success. *Manual of Patent Examining Procedure(MPEP)* § 2142; See also *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991). It is important to note that all three elements must be shown to establish a *prima facie* case of obviousness. Thus, if one element is missing, a *prima facie* case of obviousness does not exist. Furthermore, the Examiner must set forth any rejection under 35 U.S.C. §103(a) with particularity. As set forth by the Supreme Court in *KSR Int’l Co. v. Teleflex, Inc.*, No. 04-1350 (U.S., Apr. 30, 2007), the analysis supporting a rejection under 35 U.S.C. §103(a) “should be made explicit,” and it is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements” in the manner claimed. *KSR*, slip op. at 14.

a. Claims 95-96 and New Claims 114-126

Claims 95-96 and new claims 114-126 each depend from independent claim 69. There is no *prima facie* case of obviousness as to these claims because Dangman in view of Houze does not teach or suggest each limitation of the claimed invention. In particular, there is no teaching or suggestion in either of these references to provide for the specific molar ratio of dye:basic reagent set forth in these claims. Nor is there any suggestion or motivation in Dangman and Houze to provide for the claimed combination of basic reagents and dyes. Dangman and Houze pertain to nonanalogous arts – medical gloves and bioadhesive compositions, respectively. Because these pertain to nonanalogous art, it is unlikely that a person of ordinary skill in the art, seeking a method for disinfecting or sterilizing a medical device, would be motivated by Houze to provide for the claimed methods.

The Patent Office has set forth its position regarding *KSR Int'l. Co. v. Teleflex, Inc.*, discussed *supra*, noting that in formulating a rejection under 35 U.S.C. §103(a) based on a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the claimed manner. In the instant case, no specific reason has been set forth.

In view of the foregoing, there is no *prima facie* case of obviousness as to claims 95-96 or new claims 114-115.

b. Claims 99-100 and New Claims 127-129

Claims 99-100 and new claims 127-129 each depend from claim 74. There is no *prima facie* case of obviousness as to any of these claims because Dangman in view of Houze fails to teach or suggest each limitation of the claimed invention. In particular, neither Dangman nor Houze teaches or suggests any of the specific molar ratios of basic reagent:dye set forth in these

claims. Nor do these references teach or suggest any method of disinfection or sterilization of any fluid.

Nor would one of ordinary skill in the art be motivated to provide for the invention set forth in the claims based on the teachings of Dangman and Houze. Dangman, as discussed above, pertains to certain protective medical gloves and methods for their use, and Houze certain bioadhesive compositions for optical administration of active agents (see, *e.g.*, abstract). They are from nonanalogous arts. Further, the references to chlorhexidine and gentian violet in Houze are isolated, and are set forth among a list of hundreds of what are referred to as “active agents.” See Houze, [0085]-[0373].

It is the Examiner’s responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Intl*, 745 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). Furthermore, the analysis supporting a rejection under 35 U.S.C. §103(a) “*should be made explicit*,” and it is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements” in the manner claimed. *KSR*, slip op. at 14 (emphasis added). No such explicit teaching or suggestion can be found in these references.

In view of the foregoing, it is respectfully submitted that claims 99-100 are patentable over Dangman in view of Houze.

c. Claim 105 and New Claims 130-134

Claim 105 and new claims 130-134 depend from claim 103. As to these claims, there is no *prima facie* case of obviousness because Dangman in view of Houze fails to teach or suggest each limitation of the claimed invention. In particular, neither Dangman nor Houze teach or

suggest any of the dyes set forth in claim 105 or new claims 130-134. Nor is there any teaching or suggestion to one of ordinary skill in the art to provide for the specific molar ratios of dye:basic reagent set forth in these claims. Therefore, in the absence of any teaching or suggestion of each limitation of the claimed invention, there can be no *prima facie* case of obviousness.

d. Claims 109-111

Claims 109-110 pertain to methods for disinfecting and/or sterilizing a wound. There is no *prima facie* case of obviousness as to these claims because there is no teaching or suggestion in the cited prior art references pertaining to the specific molar ratio of basic reagent:dye set forth in the claims. Therefore, in the absence of any teaching or suggestion of each limitation of the claimed invention, there can be no *prima facie* case of obviousness.

3. Rejections Based on Dangman In View of Kirk-Othmer Encyclopedia

Claims 7-8, 96-97, 101-102, and 108 are rejected under 35 U.S.C. §103(a) as being unpatentable over Dangman as applied above and further in view of Kirk-Othmer Encyclopedia. In view of the amendment set forth herein cancelling certain claims without prejudice or disclaimer, the only claims at issue in this rejection include claims 96-97, 101-102, and 108. There is no *prima facie* case of obviousness because Dangman in view of Kirk-Othmer Encyclopedia fails to teach or suggest each limitation of the claimed invention.

a. Claims 96-97 and New Claims 114-126

Claims 96-97 and new claims 114-126 each depend from independent claim 69. As to these claims, there is no *prima facie* case of obviousness because the cited combination of references does not teach or suggest each limitation of the claimed invention. In particular, Dangman in view of Kirk-Othmer does not teach or suggest any of the specific ratios of basic reagent:dye set forth in the claims. Further, as to claims reciting “brilliant green,” the Examiner

has not established that Dangman or Kirk-Othmer provide any teaching or suggestion to provide for brilliant green. Applicants invite the Examiner to specifically point out any teaching or suggestion in either reference pertaining to brilliant green dye. Therefore, in the absence of a teaching or suggestion pertaining to each limitation of the claimed invention, there can be no *prima facie* case of obviousness.

b. Claims 101-102 and New Claims 127-129

Claims 101-102 and new claims 127-129 each depend from claim 74. There is no *prima facie* case of obviousness as to these claims because Dangman in view of Kirk-Othmer fails to teach or suggest each limitation of the claimed invention. In particular, neither reference teaches or suggests disinfection or sterilization of any fluid. Further, as discussed above, Applicants find no disclosure in these references pertaining to brilliant green, or any of the specific molar ratios of basic reagent:dye set forth in these claims.

In view of the foregoing, it is respectfully submitted that claims 101-102 are not unpatentable under 35 U.S.C. §103(a) over Dangman in view of Houze.

c. Claim 108 and New Claims 130-134

Claim 108 and new claims 130-134 each depend from claim 103. There is no *prima facie* case of obviousness because Dangman in view of Kirk-Othmer does not appear to teach or suggest each limitation of the claimed invention. As discussed above, Applicants have reviewed Kirk-Othmer and Dangman, and find no teaching or suggestion in either of these references pertaining to brilliant green. The Examiner has not pointed out any such teaching or suggestion in this reference with particularity, and Applicants invite the Examiner to do so. Further, there is no teaching or suggestion in either reference pertaining to the molar ratios of basic reagent:dye set forth in these claims.

In the absence of a teaching or suggestion as to each limitation of the claimed invention, there can be no *prima facie* case of obviousness. Therefore, it is respectfully requested that this rejection should be withdrawn.

d. Claim 98

As set forth in the Examiner's Interview Summary dated February 22, 2007, the Examiner has indicated that claim 98 should have been listed in the same rejection as claim 97 (Dangman in view of Kirk-Othmer) "because Dangman clearly teaches the use of chlorhexidine." Statement of Substance of Interview dated February 22, 2007.

Applicant notes that the Examiner has failed to set forth an analysis supporting the rejection in accordance with the requirements set forth by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, No. 04-1350 (U.S., Apr. 30, 2007). In particular, the Court noted that the analysis supporting a rejection under 35 U.S.C. §103(a) should be made explicit, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. *KSR*, slip op. at 14. More particularly, the Court noted that "[o]ften, it will be necessary ... to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an *apparent reason* to combine the known elements in the fashion claimed by the patent at issue," and that "[t]o facilitate review, this analysis *should be made explicit*." *Id.*, (emphasis added).

The Examiner has failed to set forth any explicit reason for combining the references. She appears to indicate that there is motivation because Dangman is said to teach chlorhexidine. However, she fails to set forth any apparent reason as to why one of ordinary skill in the art

would combine brilliant green with chlorhexidine. The Office Action provides no detail regarding how, if at all, Kirk-Othmer or Dangman teaches or suggests any composition that includes brilliant green. Thus, because the analysis set forth by the Examiner is not in accordance with the requirements set forth in *KSR*, the rejection is improper.

Applicants note, as discussed above, that the Court in *KSR* did not totally reject the use of “teaching, suggestion, or motivation” as a factor in the obviousness analysis. *KSR*, slip op. at 14-15. There is no *prima facie* case of obviousness because the Examiner has not established that Dangman in view of Kirk-Othmer teaches or suggests each limitation of the claimed invention. As discussed above, there is no teaching or suggestion pertaining to any composition that includes brilliant green, or any composition that includes brilliant green in combination with chlorhexidine, or any composition that includes the specific recited molar ratio of chlorhexidine to brilliant green. Therefore, it is respectfully requested that claim 98 is not unpatentable under 35 U.S.C. §103(a) based on Dangman in view of Kirk-Othmer.

4. Rejections Based on Harper

Claims 75-77 are rejected under 35 U.S.C. §103(a) as being unpatentable over Harper as applied above.

There is no *prima facie* case of obviousness because Harper fails to teach or suggest each limitation of the claimed invention. In particular, Harper fails to teach or suggest any of the combinations of dye or basic reagents set forth in these claims. Harper is cited as allegedly teaching compositions comprising an indigoid dye; however, claims 75-77 do not recite such a dye. Further, Harper does not teach or suggest any of the molar ratios of dye:basic reagent set forth in the claims.

New claims 114-126 would not be rendered obvious by Harper because these claims depend from claim 69, which was considered by the Examiner to be nonobvious since it was not

included in this rejection. New claims 127-129 depend from independent claim 74, the same claim from which claims 75-77 depend. For the reasons discussed above regarding claims 75-77, there is no *prima facie* case of obviousness. Lastly, new claims 130-134 are nonobvious because they depend from claim 103, which was not included in this rejection and thus considered nonobvious by the Examiner.

In view of the foregoing, there is no *prima facie* case of obviousness of claims 75-77 or any of the new claims under 35 U.S.C. §103(a) based on Harper. Therefore, it is respectfully requested that this rejection should be withdrawn.

5. Applicants' Methods Are Synergistic Compared to Methods Using Dye Alone or Basic Reagent Alone

Even if the Examiner argues that a *prima facie* case of obviousness has been made, which Applicants as discussed above assert is not the case, Applicants would still overcome any obviousness rejection because Applicants' methods are surprisingly and unexpectedly superior compared to methods using either dye alone or basic reagent alone.

The Example section of the above-referenced patent application provides strong evidence of synergy of gentian violet (GV) and chlorhexidine (CHX) as an antiseptic/disinfectant. Table 2 and Table 3 on page 20 of the referenced patent application show zones of inhibition (ZOI) produced by coated endotracheal PVC tubes (using DCM or MeOH). As set forth in the application on page 20, lines 16-19, "endotracheal PVC tubes impregnated with Gendine (GN) are far more effective against all organisms when compared with those impregnated with CHX, and more effective than PVC tubes impregnated with GV against *Pseudomonas aeruginosa*."

Table 4 on page 21 of the referenced application shows ZOI produced by coated silicone catheters. Page 21, lines 10-12 states that "data in Table 4 shows how silicone catheters

impregnated with GN are more effective in inhibiting *MRSA*, *PS* and *C. parapsilosis* than catheters impregnated with either GV or CHX.”

Table 5, on page 21 of the present application, shows ZOI produced by coated polyurethane catheters (PU). Page 21, lines 24-27 states that “PU catheters impregnated with GN are more effective than PU catheter impregnated with GV in inhibiting *Pseudomonas aeruginosa*, and more effective than PU catheters impregnated with CHX against all three organisms, *MRSA*, *PS* and *C. parapsilosis*.”

Table 6, on page 22 of the present application, shows ZOI produced by coated silk sutures. Page 21, lines 10-12 provides that “silk sutures coated or impregnated with GN are significantly more effective in inhibiting *MRSA*, *PS* and *C. parapsilosis* than sutures coated with either GV or CHX.”

Similarly, Tables 7-10 on pages 24-25 show similar synergy against various bacterial and fungal organisms, when GV was combined with other basic reagents on the surfaces of medical devices.

Furthermore, as set forth in the Declaration of one of the inventors, Dr. Issam Raad (filed with the response to the Office Action dated January 11, 2006), additional evidence was provided demonstrating that the combination of a basic reagent and a dye has antiseptic ability as a mouthwash, coating of a glove, or coating of a catheter than is more than additive compared to either dye alone or basic reagent alone.

In addition, attached is a second Declaration of Dr. Issam Raad (“the Second Declaration; Exhibit A), which sets forth as a summary of data from his laboratory that further demonstrates a high level of synergy of the combination of a basic reagent and a dye in antiseptic ability. Second Declaration, ¶8 and Exhibit 1 of Second Declaration.

Dr. Raad notes that the most serious forms of catheter related bloodstream infections are those caused by fungi, particularly *Candida albicans*. Second Declaration, ¶9. This is the infection with the highest mortality rate – around 40%. *Id.* His laboratory team found that gendine (GV and CHX) mixed in a specific molar ratio to coat catheters and devices provides unexpectedly superior synergy against *Candida albicans*. *Id.* The strain used in the studies summarized in Exhibit 1 was obtained from a patient who suffered from catheter-related fungemia/candidemia caused by *Candida albicans* (strain 009-3072). *Id.* In the first part of the study summarized in Exhibit 1, they calculated a minimal inhibitor concentration (MIC) and minimal fungicidal concentration (MBC) for each of the components, GV and CHX. The MIC/MBC was 0.5 microgram per mL for the GV and 16 microgram per mL for CHX. *Id.*

Dr. Raad's group then tested for synergy of the combination of CHX and GV over a range of 1:1 to 100:1, and obtained the results described on page 2 of Exhibit 1. Second Declaration, ¶10. Boxes that are shaded had a complete kill of the *Candida albicans* at the respective concentrations of the components that are lower than the MIC and MBC of CHX alone and GV alone. *Id.* The best synergistic data was obtained at a ratio of CHX:GV of 1:1 and 10:1, with a plateauing effect at 25:1 and thereafter. *Id.* In other words, Dr. Raad's team found that there is synergy obtained at 50:1 and 100:1 but it is not appreciably different from 25:1. *Id.*

As noted by Dr. Raad, these results clearly establish that the claimed methods using a combination of a dye and basic reagent are surprisingly and unexpectedly superior compared to methods of disinfecting using dye alone or basic reagent alone. Second Declaration, ¶11.

Further, Dr. Raad's group has published a study (Bahna *et al.*, Oral Oncol. 2007 Feb.; 43(2):159-64; Exhibit 2) that demonstrates that mouthwash compositions that have a ratio of dye:basic reagent of 10:1-66:1 demonstrated synergistic antimicrobial efficacy against free-

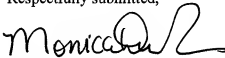
floating and biofilm forms of *Candida albicans*. Second Declaration, ¶12

Thus, any *prima facie* case of obviousness has been successfully rebutted.

E. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Monica A. De La Paz", with a stylized flourish at the end.

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EXHIBIT A